

# A New Antituberculosis Drug?

By ROBERT J. ANDERSON, M.D.

Announcement of the use of isonicotinic acid hydrazide (isoniazid) in the treatment of tuberculosis caused immediate and widespread reactions. The reports, published by New York newspapers at the end of February 1952, were accepted by the public with understandable enthusiasm. The professional attitude, however, was one of cautious open-mindedness. Aware that the limited clinical trial of the new drug was insufficient, the professional societies concerned at once warned the public against undue optimism.

"The introduction of a new drug in the therapy of tuberculosis is likely to raise more questions for a few years than it will answer. There is no knowledge at the present time that isonicotinic acid hydrazide or its isopropyl derivative will accomplish more than has been accomplished with streptomycin and PAS. It may prove to be an additional drug of great value. It may be years before its exact contribution to the therapy of tuberculosis can be assessed accurately." Thus spoke the American Trudeau Society.

The American College of Chest Physicians observed: "There has not been enough work or enough cases treated to be able to determine how this drug will fit into the present-day treatment of tuberculosis. If all the promise of effectiveness is fulfilled, this drug can do no more than add another weapon to those already used by

chest specialists in the treatment of tuberculosis. Whether this drug will extend the scope of treatment, decrease the time required, or change the approach to certain types of the disease has yet to be determined. It appears to hold great promise but should not be used as regular treatment in new cases until a great deal more is known about it and its reaction in the human being."

## Cooperative Research

Seeking answers to such questions, and to others, the Division of Chronic Disease and Tuberculosis is conducting a comparative research project in cooperation with 22 tuberculosis hospitals. To evaluate the new drug, comparisons are being made between results obtained with isoniazid, alone and in combination with streptomycin, and results of treatment with a combination of streptomycin and PAS (para-aminosalicylic acid).

We hope to learn the comparative effectiveness of the new drug on the forms of pulmonary tuberculosis which comprise the majority of cases in this country. The study is planned not only to measure the influence of the different regimens on weight, temperature, disappearance of the bacillus, and X-ray changes, but also to learn about organisms resistant to the drugs, the success or failure of treatment, and death rates. We are particularly interested in knowing whether isoniazid will be useful for streptomycin-sensitive patients and those with streptomycin-resistant bacilli. Among 1,100 patients treated in the first 5 months of the study, 40 percent were streptomycin-resistant.

The pattern of cooperative research we are using is one which the Division of Tuberculosis

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developed in 1949 for testing streptomycin therapy. A similar research project in 1950 studied the combined effect of streptomycin and PAS, a combination now widely used against tuberculosis. A number of hospitals pool their cases and cooperate in one coordinated investigation. In a relatively short time observations on groups of comparable cases can be assembled in numbers large enough to yield decisive results.

The protocol of the isoniazid study was agreed upon in advance by the participating clinicians, who report their observations every 4 weeks to our office, where they are analyzed statistically. The names of patients to be included in the study are submitted to the central office in order that the patients may be placed on a treatment course which is determined by random allocation. Each patient is placed on one of the drug regimens, and will receive such other treatment as his physician prescribes. Only patients with X-ray evidence of pulmonary tuberculosis and positive bacteriology are eligible, and provision has been made to keep the welfare of the patients paramount without jeopardizing the validity of the study. Each will be treated with the drugs for 40 weeks and watched for an additional 24 weeks.

### **Future Implications**

Until studies such as this are completed, any comments about the future implications of isoniazid must necessarily be highly speculative. We are dealing with a chronic disease of very long course, characterized by a wide range of possible manifestations, slow response to therapy, relapses, and prolonged treatment. Until much more evidence is in, we can only hazard guesses. The effect of isoniazid and the permanency of that effect on the patient's disease have not yet been determined. Drug-resistant bacilli already have been reported. There are many other important questions still unanswered. On the other hand, we must be alert to utilize even partial knowledge of the drug; even interim findings may be valuable.

Even in the event that the new drugs prove to be extremely efficacious, the program of tuberculosis control through public health measures will not be altered appreciably, in my judg-

ment. The principal effects of isoniazid most probably will be to make case finding and hospitalization even more urgent.

Isoniazid brought tuberculosis dramatically to the attention of the general public, many of whom believed the disease had been vanquished years ago. I think we would be wise to make capital of the renewed interest in tuberculosis which announcement of the drug has stimulated. If isoniazid disappoints us, as other therapies have disappointed us and our patients in the past, the extra vigor we invest now in case finding will tend to offset the let-down in public interest which may come in the future. And if isoniazid lives up to its early promise, as we all hope, surely we will want to strengthen and extend our efforts, so that all who need it may have the new treatment.

The implications of isoniazid for hospitals are not clear at this early stage. But if we assume that no toxic properties will be revealed and that resistance can be dealt with, then the properties claimed for the drug—that it reduces fever and restores appetite—alone would make it useful. If therapy with isoniazid requires less time than present therapeutic methods, turn-over in hospitals could conceivably be rapid. To the extent that it shortens the length of patient stay, the new drug could reduce the number of hospital beds needed.

Effective as they are in preventing or postponing death, streptomycin and PAS prolong hospital stay and also cause more patients to seek hospital care. In addition, some patients are so benefited that other forms of therapy, including surgery, can be employed. Therefore, unless it is rapid in action, an improved therapy very probably would aggravate the shortage of tuberculosis beds. For the same reasons, the number of cases requiring supervision by health departments would be increased correspondingly.

### **Measuring Control**

The assertion is sometimes made that tuberculosis is a disappearing disease in this country. In large part, such views are based on the trend of mortality, which has been dramatically downward. Nevertheless, tuberculosis remains the seventh leading cause of death and the only

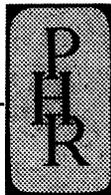
communicable disease among the first 10 causes of death. In the age group 15 to 34, tuberculosis is the leading cause of death from disease. From the standpoint of mortality then, the "disappearance" of tuberculosis seems to have been more advertised than achieved.

In any event, the dimensions of the tuberculosis control problem are seen more realistically when viewed in the light of morbidity data. The best estimate is that there are now 1,200,000 people in this country with tuberculosis, who may be placed in four groups. First there are the 500,000 persons with tuberculosis who are known to their health departments. Half of these are active cases. In addition, an estimated 700,000 persons with either active or inactive tuberculosis are not known to any health department.

Only 105,000 of the 250,000 persons known to have active tuberculosis are in hospitals now. Among the 145,000 known active cases of tu-

berculosis who are not hospitalized are 40,000 persons with positive sputum. These are the patients for whom additional beds are urgently needed. Then there are about 30,000 persons whose tuberculosis seems to be progressing, according to X-ray, although their sputum was negative when last tested. The remaining 75,000 persons with known active tuberculosis who are at home have not had a sputum examination reported during the past year.

Whether mortality or morbidity is used as a measure, tuberculosis is still far from controlled in the United States, despite all of the efforts directed against it by the health professions. To deal with a public health problem of this magnitude, the Nation obviously needs more tuberculosis beds, more clinics and equipment, more and better-trained health department personnel. The development of improved therapeutic methods emphasizes these pressing needs.



### **Trend in Hospital Utilization, 1951**

A new high in hospital admissions was reached in the United States in 1951, according to the report on hospital services by the Council on Medical Education and Hospitals of the American Medical Association. During the year, 18 million patients were admitted to 6,637 hospitals, a rate of one every 1.75 seconds. More than 427 million patient-days of care were recorded.

Hospital births also set new records in 1951. Three million births, almost 90 percent of the total recorded, took place in hospitals, the association report states.